Electrophysiological and hemodynamic effects of vernakalant and flecainide during cardiac resynchronization in dyssynchronous canine hearts

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Abstract: INTRODUCTION: Patients with heart failure and left bundle branch block (LBBB) are frequently treated with biventricular pacing (BiVP). Approximately one-third of them suffer from atrial fibrillation. Pharmacological conversion of atrial fibrillation is performed with drugs that slow ventricular conduction, but the effects of these drugs on the benefit of BiVP are poorly understood. METHODS: Experiments were performed in dogs with chronic LBBB, investigating the effects of Vernakalant and Flecainide (n = 6 each) on hemodynamics and electrophysiology during epicardial (EPI) and endocardial BiVP. The degree of dyssynchrony and conduction slowing was quantified using QRS width and EPI electrical mapping. RESULTS: Compared with LBBB, EPI and endocardial BiVP reduced QRS duration by 7% ± 9% ($P < 0.05$ compared with LBBB) and 20% ± 13% ($P < 0.05$ compared with LBBB, $P < 0.05$ between modes), respectively. During BiVP, the administration of Vernakalant and Flecainide increased QRS duration by 20% ± 14% ($P < 0.05$ compared with predrug BiVP) and 34% ± 10% ($P < 0.05$ compared with predrug BiVP, $P < 0.05$ between drugs). left ventricular (LV) dP/dtmax decreased by 16% ± 8% ($P < 0.05$ compared with predrug BiVP) during Vernakalant and by 14% ± 15% ($P < 0.05$ compared with predrug BiVP) during Flecainide. The drugs did not affect the relative changes in QRS width and LV dP/dtmax induced by BiVP. CONCLUSIONS: Vernakalant and Flecainide decrease contractility, slow myocardial conduction velocity, and increase activation time. The electrical and hemodynamic benefits of BiVP are not altered by the drugs.

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Electrophysiological and Hemodynamic Effects of Vernakalant and Flecainide During Cardiac Resynchronization in Dyssynchronous Canine Hearts

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Introduction: Patients with heart failure and left bundle branch block (LBBB) are frequently treated with biventricular pacing (BiVP). Approximately one-third of them suffer from atrial fibrillation. Pharmacological conversion of atrial fibrillation is performed with drugs that slow ventricular conduction, but the effects of these drugs on the benefit of BiVP are poorly understood.

Methods: Experiments were performed in dogs with chronic LBBB, investigating the effects of Vernakalant and Flecainide (n = 6 each) on hemodynamics and electrophysiology during epicardial (EPI) and endocardial BiVP. The degree of dyssynchrony and conduction slowing was quantified using QRS width and EPI electrical mapping.

Results: Compared with LBBB, EPI and endocardial BiVP reduced QRS duration by 7% ± 9% ($P < 0.05$ compared with LBBB) and 20% ± 13% ($P < 0.05$ compared with LBBB, $P < 0.05$ between modes), respectively. During BiVP, the administration of Vernakalant and Flecainide increased QRS duration by 20% ± 14% ($P < 0.05$ compared with predrug BiVP) and 34% ± 10% ($P < 0.05$ compared with predrug BiVP, $P < 0.05$ between drugs). left ventricular (LV) dP/dtmax decreased by 16% ± 8% ($P < 0.05$ compared with predrug BiVP) during Vernakalant and by 14% ± 15% ($P < 0.05$ compared with predrug BiVP) during Flecainide. The drugs did not affect the relative changes in QRS width and LV dP/dtmax induced by BiVP.

Conclusions: Vernakalant and Flecainide decrease contractility, slow myocardial conduction velocity, and increase activation time. The electrical and hemodynamic benefits of BiVP are not altered by the drugs.

Key Words: Vernakalant, Flecainide, cardiac resynchronization therapy, dyssynchrony, atrial fibrillation

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INTRODUCTION

Cardiac resynchronization therapy (CRT) has been shown to reduce morbidity and mortality in patients with mild to severe heart failure (HF) and dyssynchrony.[1] Despite CRT's improvement in symptoms and left ventricular ejection fraction, the risk of developing paroxysmal or persistent atrial fibrillation (AF) remains high.[2] This encompasses the clinical dilemma whether patients who show increase in left ventricular ejection fraction and a reduction in ventricular volumes (in some cases even normalization) may be treated with antiarrhythmic drugs, such as Flecainide or Vernakalant, for pharmacological cardioversion because both are contraindicated in HF.[3,4] Both drugs are indeed capable of rapidly converting recent-onset AF into sinus rhythm,[5] whereas Flecainide can also be used to prevent episodes of paroxysmal AF after direct current cardioversion.[6,7] Compared with Flecainide, Vernakalant is relatively atrial selective; it acts on all phases of the action potential by blocking the potassium currents I_{Kur}, IK_{ACh}, I_{kr}, and I_{to} and the sodium channel I_{Na}, but it has little effect on the I_{K1} and I_{Ks} receptors.[8] Thus, at least in theory, Vernakalant may be preferred to Flecainide in patients with moderate left ventricular (LV) dysfunction.

Clinical evidence about interference of Vernakalant and Flecainide with CRT is not available because these patients are commonly excluded in AF studies. Therefore, it is clinically relevant to test, in a preclinical model, the potential interference of antiarrhythmic drugs with the positive inotropic effect elicited by CRT.

In the present study, we investigated the effects of Vernakalant and Flecainide, during acute biventricular pacing (BiVP), on ventricular function and conduction in an established canine model of chronic dyssynchrony presenting with moderately depressed left ventricular systolic function.[9] Extensive electrical mapping and hemodynamic measurements were performed before and after infusion of either Vernakalant or Flecainide during conventional epicardial (EPI) and novel endocardial (ENDO) BiVP. We tested both pacing modalities because our previous studies showed that ENDO BiVP activates the LV in a more physiological manner and further improves LV function when compared with EPI BiVP.[10,11]

METHODS

Animal handling was performed according to the Dutch Law on Animal Experimentation and the European Directive

for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (86/609/EU). The protocol was approved by the Experimental Animal Committee of Maastricht University.

Experimental Models

The experiments were performed on 12 adult mongrel dogs of either sex, weighing 21.7 ± 4.4 kg. After induction with sodium thiopental, anesthesia was maintained by continuous infusion of Midazolam (0.25 $mg \cdot kg^{-1} \cdot h^{-1}$) and Sufentanil (3 $\mu g \cdot kg^{-1} \cdot h^{-1}$). During a sterile closed-chest procedure, left bundle branch block (LBBB) was induced by radiofrequency ablation as described in detail previously.[12] Final experiments were performed 16–18 weeks after the onset of LBBB. At that time, the animals were given the same anesthesia as used during the first procedure.

Experimental Methods

Right ventricular (RV) and LV pressures were measured by a 7-Fr catheter tip manometer (CD-Leycom, Zoetermeer, the Netherlands). An RF Marinr catheter (Medtronic, Heerlen, the Netherlands) was advanced into the right atrium to pace at a fixed atrial rate (atrial paced, atrial sensed, inhibited pacing) at approximately 10 beats per minute above the intrinsic rhythm. Surface electrocardiogram (ECG) was derived from the limb leads.

After a thoracotomy, 2 multielectrode arrays containing 102 electrodes were placed epicardially. The first array was placed around the base of the heart, and the second was placed around the mid level. Both the arrays were used to measure local RV and LV electrograms. One of the electrodes positioned at the mid level of the LV free wall was used as EPI pacing electrode. Its 4 neighboring electrodes were used to calculate conduction velocity. In addition, an ENDO plunge electrode was placed at the mid LV lateral wall for ENDO pacing. Apical electrograms were measured by a small array of 4 electrodes. A multielectrode catheter (Daig Livewire TC, Minnetonka, MN) was positioned in the RV to record septal electrograms and simultaneously pace the RV apex.

Infusion Protocol

Dogs were arbitrarily assigned to receive Vernakalant (n = 6) (MSD, West Point, PA) or Flecainide (n = 6) (Meda Pharma B.V., Amstelveen, the Netherlands). Both the drugs were given in a 2-dose regime. The first dose of Vernakalant was given using slow infusion of 5.7 mg/kg in 15 minutes, followed by an interval of 15 minutes before the second dose. The second dose contained 2.3 mg/kg and was similarly given over a 15-minute period. The aim of the split dosing regimen was to achieve the target dose within 15 minutes and maintain this target for the next 45 minutes. To verify concentration levels of Vernakalant, plasma samples were collected right after the first and second doses and analyzed at Cardiome Pharma Corp (Vancouver, Canada). The first dose of Flecainide, 1.5 mg/kg, was administered over a 10-minute period. The second dose, 2.5 mg/kg, was given correspondingly, after a 15-minute interval. These doses are comparable with the previously used concentrations of Flecainide in canine experimental models and are expected to reach a concentration of 1.8×10^{-5} mM.[13,14]

Hemodynamic status was continuously monitored throughout the protocol. Five minutes before the administration of both the drugs and within 5 minutes after final administration, hemodynamic and electrophysiological effects of BiVP were assessed and compared with LBBB (AAI pacing). BiVP was performed by pacing the RV apex either in combination with an EPI electrode on the LV mid lateral wall (EPI BiVP) or in combination with the LV ENDO electrode (ENDO BiVP). A fixed short AV delay (80–100 ms) was chosen to ensure full capture. VV interval was set to 0 ms. ENDO BiVP and EPI BiVP were randomly assigned. Each pacing modality was allowed to stabilize for a minute before hemodynamic and electrophysiological measurements were started.

Data Analysis

Depolarization times were calculated for each individual electrode as the difference between the onset of activation (ventricular pacing artifact during BiVP or Q wave during AAI pacing) and the time of steepest negative deflection in the electrogram ($-dV/dt$). Total activation time (AT) was defined as the difference between the shortest and longest depolarization times. ECG parameters were extracted from the surface ECG. Although QRS width and total AT reflect overall electrical dyssynchrony, they do not express the spatial progression of the electrical wave front. For that purpose, AT vectors (ATV) were calculated in a short-axis circumference using the values of the depolarization times of all the electrodes.[15] The degree of dyssynchrony was expressed as the ATV amplitude (milliseconds) and the main direction of conduction as the ATV angle (degree). Angles were measured from the reference vector between the RV free wall (0 degree) anterior LV (90 degree) and LV free wall (180 degree) with the aid of custom MATLAB software (MathWorks, Natick, MA). During EPI BiVP, conduction velocity could be estimated by averaging the dividend of the ATs of 4 neighboring electrodes and their known fixed distances.[10]

Mechanical interventricular dyssynchrony (MIVD) was assessed from the time difference of the upslope of normalized LV and RV pressures.[12] Hemodynamic data were analyzed as described previously with the aid of custom MATLAB software.[16] LV dP/dtmax, the maximal first derivative of LV pressure, is a common index of contractility.

Statistical Analyses

Data are presented as mean ± SD. Statistical analysis was performed using Statistical Package for Social Sciences for Windows version 20.0 (SPSS Inc., Chicago, IL). The effects of EPI and ENDO BiVP after Vernakalant or Flecainide were analyzed using linear mixed-effect models. This method is also known as multilevel analysis or mixed-effect analysis. The random intercept corrects for the correlation between repeated measurements. The least squared differences correction was used for post hoc comparisons. A paired sample *t* test was used for a head-to-head comparison between ENDO and EPI BiVP neglecting drug or dose. A 2-sided

probability value of $P \leq 0.05$ was considered statistically significant.

RESULTS

Data from a previous study showed that in the animal preparation used, all electrical and hemodynamic variables are essentially constant over a 45-minute duration of the protocol (Table 1).[15] No statistical differences were noted in baseline values between the Vernakalant and the Flecainide groups.

In 11 of the 12 experiments, the effects of ENDO and EPI BiVP were evaluated at baseline and after the second dose of the drugs. One dog in the Flecainide group died during the infusion of the second dose because of cardiogenic shock.

Plasma levels of Vernakalant reached the desired exposure target of 3 μg/mL (3.7 ± 0.8 μg/mL). This concentration is equal to 1.1^{-5} mM. There was no significant difference between plasma concentrations after the first and second doses.

Electrophysiological Effects

The electrical activation map in the left panel of Figure 1 shows a typical LBBB-type activation pattern, which starts in the RV, then progresses, through to septum, around the LV, and finally activates the LV lateral basal wall. ENDO and EPI BiVP reverse this conduction pattern by early activation of the LV lateral wall from which activation spreads toward the septum colliding with the activation wave front originating from the RV apex electrode (middle and right panels).

During AAI pacing, both the drugs significantly increased QRS width (by 17% ± 13% vs. 34% ± 15% for Vernakalant vs. Flecainide) (Table 2). During BiVP, the drugs caused a similar relative increase in QRS width (20% ± 14% vs. 34% ± 10% for Vernakalant vs. Flecainide) when compared with predrug BiVP (Fig. 2, lower panel). Still, BiVP caused a similar and constant reduction in QRS width as compared with AAI pacing (Fig. 3, lower panel). ENDO BiVP reduced dyssynchrony significantly more than EPI BiVP ($P < 0.05$). Conduction velocity, calculated during EPI BiVP, was significantly reduced by Flecainide, but only a trend toward reduction was seen after Vernakalant administration (Table 2).

During AAI pacing, the ATV angle pointed toward the LV lateral wall (180 degree). The ATV angle did not change significantly after the infusion of either drug, but the ATV amplitude tended to increase after Vernakalant and increased significantly after Flecainide. BiVP changed the ATV angle toward an angle between the RV wall (0 degree) and the anterior LV wall (90 degree), indicating a main direction of conduction from the LV toward the RV. Besides a change in ATV angle, ATV amplitude decreased considerably on BiVP, reflecting a more synchronous activation pattern. After infusion of both Vernakalant and Flecainide, no significant changes were observed in either ATV angle or amplitude during BiVP (Table 2, Fig. 4).

Both the drugs prolonged intrinsic PQ time by approximately 17%. During BiVP, PQ time remained equal because a fixed AV delay was used. During AAI pacing and during BiVP, no significant effect on QT corrected for heart rate interval was observed, nor were any arrhythmias detected.

TABLE 1. Hemodynamic and Electrical Activation Data During 45 Minutes in a Historical Control Group Undergoing Various Pacing Settings

	Control	
	AAI Pacing	
	T = 0 min	T = 45 min
Heart rate, bpm	136 ± 11	144 ± 15*
QRS width, ms	97 ± 12	96 ± 15
PQ time, ms	141 ± 35	137 ± 32
QTc, ms	355 ± 17	353 ± 19
Total AT, ms	80 ± 16	82 ± 17
LV systolic pressure, mm Hg	78 ± 16	79 ± 12
LV diastolic pressure, mm Hg	3 ± 3	4 ± 3
LV dP/dtmax, mm Hg/s	1187 ± 212	1214 ± 142
LV dP/dtmin, mm Hg/s	−1199 ± 320	−1277 ± 303
RV systolic pressure, mm Hg	23 ± 12	26 ± 13
RV diastolic pressure, mm Hg	8 ± 5	8 ± 4

*$P < 0.05$ compared with T = 0 min.

Hemodynamic Effects

Associated with the slower electrical conduction induced by the drugs, MIVD increased significantly after Flecainide and tended to increase after Vernakalant. Conversely, BiVP lowered MIVD, indicating mechanical resynchronization. This mechanical resynchronization was more pronounced for ENDO BiVP than for EPI BiVP (Table 2).

During AAI pacing, Vernakalant and Flecainide decreased LV dP/dtmax by 17% ± 4% and 15% ± 9%, respectively. Similar relative reductions in LV dP/dtmax were noted during EPI and ENDO BiVP, with decreases of 16% ± 8% in the Vernakalant group and 14% ± 15% in the Flecainide group (Table 3, Fig. 2). BiVP increased LV dP/dtmax by approximately 15%, independent of the presence, dose, and kind of drug (Fig. 3), the absolute increase being 127 ± 26 mm Hg/s during EPI BiVP and 161 ± 44 mm Hg/s during ENDO BiVP. Combining data collected during the administration of both drugs, LV dP/dtmax increased significantly more during ENDO than during EPI BiVP ($P < 0.05$).

EPI and ENDO BiVP had no significant influence on LV systolic pressure (Table 3). Vernakalant decreased LV systolic pressure to levels slightly, but not significantly, below predrug values, whereas Flecainide did decrease LV systolic pressure significantly below predrug values. Nevertheless, even for Flecainide, the reduction in LV systolic pressure was modest with an average decrease of 5 mm Hg (Table 2).

Both drugs reduced LV dP/dtmin and Tau, an index of LV isovolumic relaxation, but this was hardly affected by ENDO or EPI BiVP (Table 3). Effects of both drugs on RV pressure were small (Table 1). EPI and ENDO BiVP caused an insignificant reduction in RV systolic pressure (Table 2).

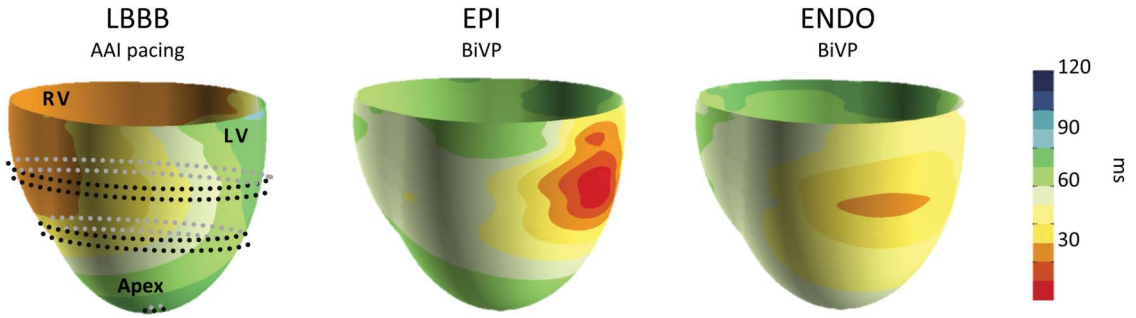

FIGURE 1. Activation maps derived from the EPI electrode arrays and plotted on a 3D model of the LV and RV epicardium as previously reported.[10] Dotted circles represent the EPI electrode arrays. Typical examples are shown of a dyssynchronous activation pattern during LBBB (left panel) and a more synchronous activation pattern during EPI BiVP (middle panel) and ENDO BiVP (right panel) at baseline.

TABLE 2. Hemodynamic and Electrical Activation Data During ENDO and EPI BiVP After Infusion of Vernakalant and Flecainide

	Vernakalant					
	AAI Pacing		EPI BiVP		ENDO BiVP	
	Predrug	Drug	Predrug	Drug	Predrug	Drug
Heart rate, bpm	147 ± 3	147 ± 3	147 ± 3	149 ± 5	148 ± 3	145 ± 9
QRS width, ms	89 ± 3	103 ± 10*	84 ± 12	94 ± 12*	76 ± 13	87 ± 10*
QTc, ms	350 ± 10	361 ± 9	360 ± 16	372 ± 10	350 ± 20	369 ± 24
Total AT, ms	90 ± 10	96 ± 3*	73 ± 8	81 ± 12	70 ± 18	65 ± 9
Conduction velocity, m/s	NA	NA	0.85 ± 0.10	0.79 ± 0.12	NA	NA
ATV angle, degree	178 ± 8	179 ± 10	84 ± 62	87 ± 68	60 ± 58	43 ± 50
ATV amplitude, ms	63 ± 10	69 ± 10	35 ± 21	39 ± 25	27 ± 16	24 ± 15
MIVD, ms	−18 ± 1	−22 ± 3	−12 ± 8	−15 ± 11	−8 ± 3	−1 ± 3‡
LV systolic pressure, mm Hg	86 ± 15	82 ± 16	81 ± 14	77 ± 16*	82 ± 14	79 ± 18*
LV end diastolic pressure, mm Hg	8 ± 1	9 ± 2*	8 ± 4	8 ± 3	7 ± 3	7 ± 2
LV dP/dtmax, mm Hg/s	1257 ± 373,373	1054 ± 336*	1346 ± 257	1208 ± 218*	1414 ± 493	1249 ± 234*
LV dP/dtmin, mm Hg/s	−1494 ± 404	−1236 ± 433*	−1359 ± 420	−1224 ± 460*	−1363 ± 417	−1238 ± 453*
RV systolic pressure, mm Hg	48 ± 14	43 ± 11*	40 ± 7	37 ± 6*	38 ± 7	36 ± 6*
RV diastolic pressure, mm Hg	11 ± 5	12 ± 8	8 ± 4	8 ± 3	9 ± 5	10 ± 5
Tau, ms	35 ± 15	37 ± 6	38 ± 3	41 ± 5	36 ± 3	40 ± 5
	Flecainide					
	AAI Pacing		EPI BiVP		ENDO BiVP	
	Predrug	Drug	Predrug	Drug	Predrug	Drug
Heart rate, bpm	151 ± 15	150 ± 4	151 ± 16	149 ± 4	151 ± 16	150 ± 3
QRS width, ms	96 ± 13	126 ± 19*†	82 ± 13	114 ± 7*†	74 ± 11	102 ± 7*‡
QTc, ms	358 ± 30	394 ± 25	350 ± 27	364 ± 16	339 ± 24	365 ± 13
Total AT, ms	87 ± 12	117 ± 20*	70 ± 23	88 ± 16*	65 ± 19	74 ± 14*
Conduction velocity, m/s	NA	NA	0.85 ± 0.25	0.63 ± 0.12‡	NA	NA
ATV angle, degree	194 ± 18	196 ± 16	31 ± 23	34 ± 23	39 ± 35	19 ± 17
ATV amplitude, ms	58 ± 6	78 ± 11*	23 ± 8	31 ± 19	24 ± 20	19 ± 13
MIVD, ms	−32 ± 9	−37 ± 15*	−17 ± 5	−17 ± 6	−13 ± 9	−16 ± 12†
LV systolic pressure, mm Hg	77 ± 6	72 ± 6*†	78 ± 4	74 ± 6*	78 ± 4	75 ± 5*
LV end diastolic pressure, mm Hg	13 ± 5	14 ± 4	9 ± 7	10 ± 8	8 ± 6	9 ± 8
LV dP/dtmax, mm Hg/s	1224 ± 323	978 ± 231*	1400 ± 400	1123 ± 303*	1443 ± 389	1131 ± 319*
LV dP/dtmin, mm Hg/s	−1382 ± 444	−1134 ± 272*	−1386 ± 465	−1205 ± 372*	−1379 ± 454	−1191 ± 387*
RV systolic pressure, mm Hg	36 ± 7	33 ± 7	33 ± 6	30 ± 7	32 ± 6	30 ± 6
RV diastolic pressure, mm Hg	8 ± 9	9 ± 8	11 ± 8	12 ± 8	10 ± 7	11 ± 7
Tau, ms	37 ± 11	41 ± 6	40 ± 13	47 ± 6	40 ± 12	48 ± 9

*$P < 0.05$ compared with predrug.
†$P < 0.05$, Flecainide compared with Vernakalant at the same dosage level.
‡$P < 0.05$, ENDO compared with EPI pacing.
NA, not available.

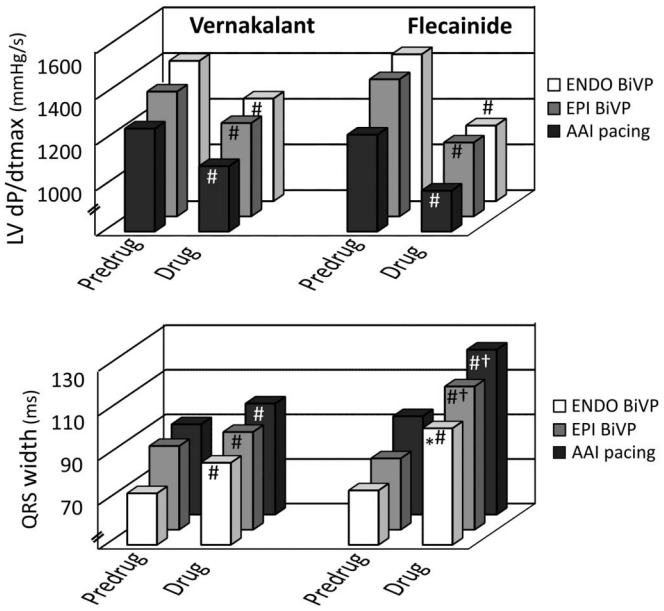

FIGURE 2. LV dP/dtmax (top) and QRS width (bottom) during intrinsic ventricular conduction (AAI pacing), EPI, and ENDO BiVP for both Vernakalant and Flecainide. Because the smallest QRS width goes hand in hand with the highest contractility, the arrangement of plotting is reversed between the top and bottom panels. SDs are mentioned in Table 1. #$P <$ 0.05 compared with predrug; †$P < 0.05$, Flecainide compared with Vernakalant at the same dosage level; and *$P < 0.05$, ENDO compared with EPI pacing.

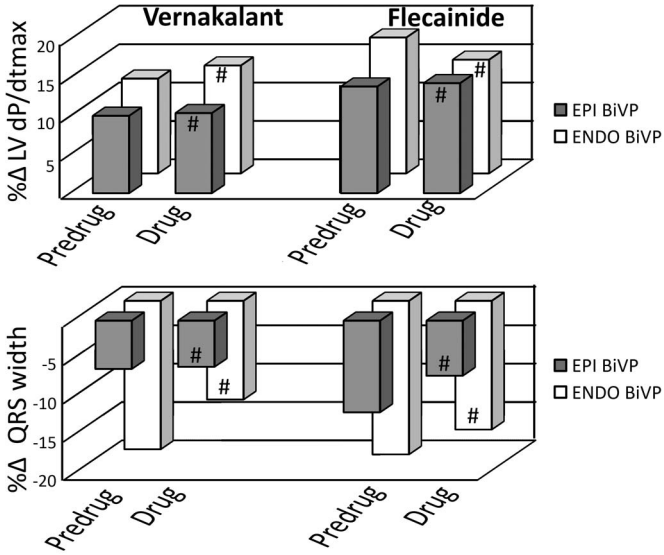

FIGURE 3. Relative increase in LV dP/dtmax (top) and QRS width (bottom) during EPI and ENDO BiVP for both Vernakalant and Flecainide with respect to LBBB (AAI pacing). SDs are mentioned in Table 2. #$P < 0.05$ compared with AAI.

Relation Between Electrical Dyssynchrony and Pump Function

The various conditions that influence electrical dyssynchrony (drugs that slow impulse conduction to a variable amount, BiVP in 2 different modes, and the combination with each other) offer the opportunity to evaluate the relation between electrical dyssynchrony and pump function over a wide range of conditions. Figure 5 depicts a close relation between QRS width and LV dP/dtmax, regardless of the way the QRS width is achieved. For example, similar LV dP/dtmax values were observed in the Vernakalant group during baseline LBBB and ENDO BiVP after drug administration.

DISCUSSION

The present study shows that, in BiV paced ventricles, Vernakalant and Flecainide slow down myocardial conduction, prolong electrical activation, and concordantly decrease LV contractility. However, the beneficial effects of both EPI and ENDO BiVP are preserved during the administration of these drugs. In all these conditions, ENDO BiVP reduces dyssynchrony more than EPI BiVP.

Electrophysiological Effects

In this canine model of proximal LBBB, the impulse conduction in the LV is entirely dependent on slow cell-to-cell conduction within the "working myocardium" rather than the rapid Purkinje system. This is true for the condition of proximal LBBB but even more for BiVP, where relatively slow cell-to-cell conduction in the working myocardium activates both the RV and the LV. The decrease in conduction velocity observed for both drugs is in line with the increase in total AT, ATV amplitude, and QRS width, whereas the unaltered ATV angle indicates that this conduction slowing occurs uniformly. The observation that neither drug significantly changed ATV amplitude during BiVP implicates that both EPI and ENDO BiVP reduce electrical dyssynchrony to a similar extent for the entire range of conduction velocities investigated.

The similar relative changes in the aforementioned variables during EPI and ENDO BiVP are interesting because a previous study demonstrated that during ENDO BiVP, a considerable part of ventricular activation occurs through early involvement of conduction through more rapidly conducting ENDO LV layers.[10] Accordingly, the data from the present study indicate that both drugs slow conduction in all layers in the LV wall to a similar extent. This implicates that Vernakalant also has a potent effect on sodium currents, which is in line with a recent study by Wettwer et al[17] that strongly suggests that the main mode of action of Vernakalant is through the blockage of sodium channels instead of the assumed more potent and atrial selective blockage of I_{Kur}.

The importance of a small ATV amplitude has been described in earlier studies of our group and is linked to optimal hemodynamic response.[15,18] The present study also supports our earlier data that ENDO BiVP is to be favored over conventionally applied EPI BiVP with respect to indices of electrical dyssynchrony and pump function.[10]

The relative increase in QRS width by Vernakalant and Flecainide observed in the present study is comparable with that in the previously reported studies that have

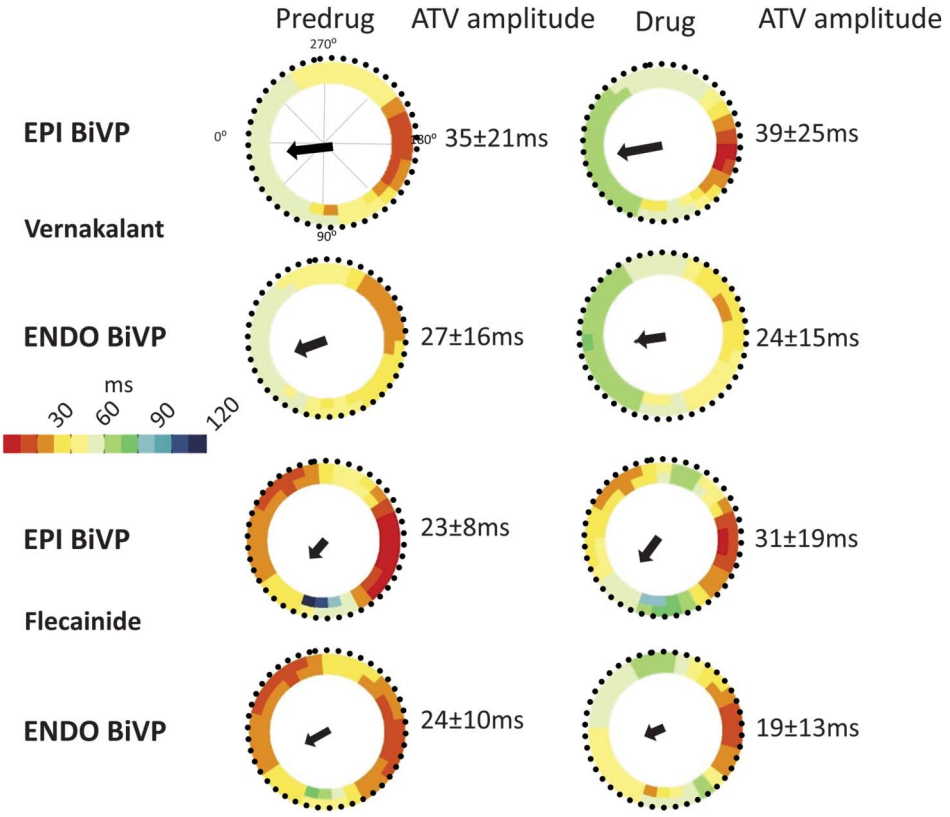

FIGURE 4. Color-coded activation sequence in a short-axis section at the level of the EPI electrode arrays as depicted in Figure 2. Data are represented as bull's-eye plots, the most basal regions being represented in the most outward layer. 0 degree and 180 degree indicate the lateral wall of the RV and LV, respectively, and 90 degree the anterior wall. Arrows represent the vector direction and amplitude, as calculated from the ATs. ATV amplitude values are mean ± SDs of the averages of the entire groups.

predominantly been performed in patients with normal ventricular conduction.[19,20] This similarity may be explained by a similar reduction in conduction velocity of the rapid Purkinje system and the working myocardium.[21] Yet, the slower conduction is likely to have stronger implications in hearts with abnormal conduction, such as during LBBB and likewise during BiVP.

Hemodynamic Effects

In the present study, 2 factors modify the electrical activation in the LBBB heart: BiVP and both drugs. It is well known that BiVP resynchronizes the heart and that this is associated with improved ventricular contractile function. The opposite holds true for Vernakalant and Flecainide because they slow down the ventricular conduction and thus

TABLE 3. Percent Difference From LBBB (AAI Pacing), MIVD, and LV End Diastolic Pressure Are Expressed as Absolute Difference

	Vernakalant				Flecainide			
	EPI BiVP		ENDO BiVP		EPI BiVP		ENDO BiVP	
	Predrug	Drug	Predrug	Drug	Predrug	Drug	Predrug	Drug
Heart rate	100 ± 0	101 ± 2	100 ± 0	101 ± 2	100 ± 0	99 ± 2	100 ± 0	100 ± 0
QRS width	94 ± 12	94 ± 10*	81 ± 14*	87 ± 10*	88 ± 16*	93 ± 9	80 ± 13*	83 ± 10*
QTc	103 ± 4	103 ± 3	99 ± 5	102 ± 7	99 ± 7	99 ± 8	97 ± 6	99 ± 10
Total AT	81 ± 8*	83 ± 11*†	71 ± 13*	67 ± 9*	69 ± 18*	77 ± 20*†	67 ± 17*	64 ± 12*
ATV direction	47 ± 37	52 ± 47	34 ± 43	27 ± 35	16 ± 11	18 ± 12	21 ± 20	10 ± 9
ATV amplitude	56 ± 20	51 ± 24	38 ± 29	26 ± 15	24 ± 16	31 ± 25	30 ± 23	22 ± 13
MIVD	7 ± 10	7 ± 9	13 ± 10	20 ± 7	16 ± 5	21 ± 12	19 ± 6	24 ± 14
LV systolic pressure	102 ± 5	99 ± 2	102 ± 6	100 ± 2	101 ± 2	103 ± 5	101 ± 3	103 ± 5
LV end diastolic pressure	1 ± 3	−1 ± 1*	1 ± 3	−1 ± 1*	−1 ± 1	0 ± 1	−1 ± 1	0 ± 1
LV dP/dtmax	110 ± 6*	110 ± 8	112 ± 9	114 ± 7*	114 ± 5*	114 ± 16	118 ± 2*	115 ± 13*
LV dP/dtmin	99 ± 4	98 ± 4	99 ± 4	100 ± 7	100 ± 4	106 ± 12	100 ± 6	105 ± 16
RV systolic pressure	93 ± 5	93 ± 5	89 ± 8	90 ± 7	92 ± 6	90 ± 8	89 ± 10	90 ± 10
RV diastolic pressure	91 ± 30	92 ± 33	110 ± 18	103 ± 51	113 ± 34	110 ± 28	101 ± 20	108 ± 29

*$P < 0.05$ compared with AAI.
†$P < 0.05$ versus ENDO BiVP.

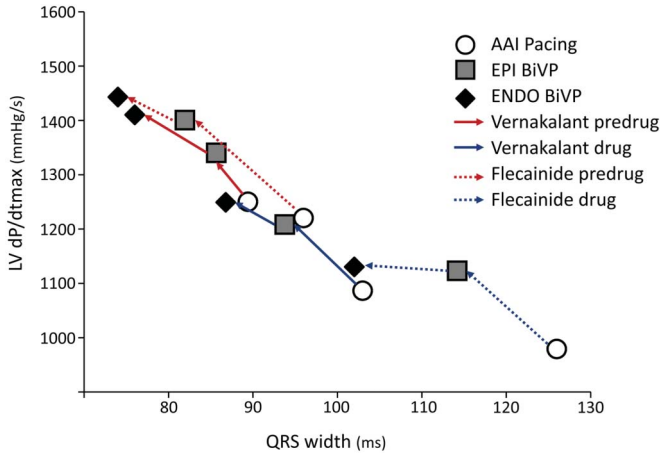

FIGURE 5. LV dP/dtmax plotted as a function of QRS width for both Vernakalant (solid lines) and Flecainide (dashed lines). For each dose, the effects of EPI BiVP (squares) and ENDO BiVP (diamonds) are linked with the baseline values during AAI pacing (circles). Red lines are linking predrug BiVP effects, whereas the blue lines link the BiVP effects after the drug. SDs are mentioned in Table 1.

effectively desynchronize the ventricles, which is associated with reduced contractility. On the other hand, sodium channel blockers may directly act negative intropic, and thus the observed decrease in contractility is potentially not related to the decrease in conduction velocity. In this regard, it is interesting that a recent study in isolated trabeculae from explanted human hearts did not find a negative inotropic effect of Vernakalant.[22] An important difference between isolated papillary muscle preparations and our in vivo model is that the muscles are field stimulated and, therefore, are not dependent on conduction. Nevertheless, BiVP can be considered to counteract the reduction in contractility that is caused by the drugs irrespective of the mechanism by which contractility is decreased. An important and interesting observation in this study is that the relative increase in LV dP/dtmax because of BiVP is not influenced by administration of the drugs. This implies that during BiVP, the tolerance for the negative effects of both drugs on dyssynchronous failing hearts may be larger. This observation is important because episodes of hypotension have been described for HF patients receiving Vernakalant and Flecainide.[23,24]

An important observation is the effects of uniformly slowed conduction velocity on paced ventricles. Although this slow conduction is created pharmacologically, it may also help to improve our insight in the effect of CRT in hearts with slow conduction by other mechanisms, such as (uniform) fibrosis or reduced expression of gap junctions. Although drug-induced increased ATs coincide with proportional reduction in contractility, the 2 modes of BiVP provide 2 "doses" of resynchronization that proportionally oppose the conduction slowing effects. One of the implications of these data may be that hearts with wider QRS complexes may require better resynchronization to achieve a good pump function, and in these hearts, ENDO CRT may thus be indicated. The other implication is that for a given mode of resynchronization, the effect is proportional to the degree of resynchronization, independent of the prevailing conduction velocity.

Comments on the Experimental Model

The chronic LBBB dog model shows moderately reduced left ventricular function and hypertrophy but is not associated with clinical symptoms of HF. This, however, best reflects the clinical situation of patients who significantly improved after CRT. On the other hand, it may explain why the drugs affect blood pressure only to a minimal amount because cardiac reserve and autonomic reflexes may compensate drug-induced hypotension.

We specifically paced at a fixed atrial rate to ascertain that the observed hemodynamic and electrical changes were not influenced by alterations in heart rate. It is also important to consider that these data have been acquired in anesthetized animals. It is not known as to whether Midazolam/Sufentanil anesthesia modulates the effects reported here or whether the effects are reproducible in awake animals.

Of course, the results of the present in vivo animal study require confirmation in patients to properly judge their clinical relevance. Furthermore, the effects of BiVP presented here are acute and serve as surrogate for the long-term alterations achieved in patients who are chronically treated with CRT.

CONCLUSIONS

Vernakalant and Flecainide decrease contractility, slow myocardial conduction velocity, and increase AT. However, the electrical and hemodynamic benefits of BiVP are not altered by the drugs, the effect being more pronounced for ENDO BiVP than for EPI BiVP.

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